CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: Cutaneous Melanoma

This report supersedes the CADTH Provisional funding algorithm report for Cutaneous Melanoma dated June 2024.

Please always check CADTH Provisional Funding Algorithms | CADTH to ensure you are reading the most recent algorithm report.

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Background

Following a request from jurisdictions, CADTH may design or update an algorithm depicting the sequence of funded treatments for a particular tumour type. These algorithms are proposals for the jurisdictions to implement and adapt to the local context. As such, they are termed "provisional." Publishing of provisional algorithms is meant to improve transparency of the oncology drug funding process and promote consistency across jurisdictions.

Provisional funding algorithms are based on 3 principal sources of information:

- CADTH pCODR Expert Review Committee (pERC) reimbursement recommendations and/or implementation guidance regarding drug place in therapy and sequencing
- implementation advice from panels of clinicians convened by CADTH concerning sequencing of drugs in the therapeutic space of interest
- existing oncology drug reimbursement criteria and legacy funding algorithms adopted by jurisdictional drug plans and cancer agencies.

Note that provisional funding algorithms are not treatment algorithms; they are neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagrams may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain jurisdictions. All drugs are subject to explicit funding criteria, which may also vary between jurisdictions. Readers are invited to refer to the cited sources of information on the CADTH website for more details.

Provisional funding algorithms also delineate treatment sequences available to patients who were never treated for the condition of interest (i.e., incident population). Time-limited funding of new options for previously or currently treated patients (i.e., prevalent population) is not detailed in the algorithm.

Provisional funding algorithms may contain drugs that are under consideration for funding. Algorithms will not be dynamically updated by CADTH following changes to drug funding status. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a CADTH provisional funding algorithm on cutaneous melanoma. However, no outstanding implementation issues were identified, and no additional implementation advice is provided in this report. The algorithm depicted herein is meant to reflect the current and anticipated funding landscape based on the previously mentioned sources of information.

History and Development of the Provisional Funding Algorithm

CADTH published the first rapid provisional funding algorithm for cutaneous melanoma in February 2023 to incorporate the recommendation for adjuvant pembrolizumab in stage IIB or IIC melanoma following complete resection. Additionally, the February 2023 algorithm incorporated other melanoma algorithms (previously developed by Cancer Drug Implementation Advisory Committee [CDIAC]) for adjuvant treatment in stage III and metastatic melanoma.

CADTH convened an implementation advice panel and published a provisional funding algorithm on cutaneous melanoma in June 2024 to address the outstanding implementation issue of downstream treatment options following nivolumab-relatlimab in the treatment of unresectable or metastatic melanoma.

Jurisdictional cancer drug programs requested an update to this rapid algorithm report in May 2024 to incorporate the latest recommendation for nivolumab (Opdivo).

Details of the relevant CADTH recommendations are outlined in Table 1, while Table 2 summarizes conclusions from the implementation advice panels.

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and Guidance on Treatment Sequencing
Stage IIB or stage IIC melanoma		

Nivolumab (Opdivo)	June 14, 2024	pERC recommends that nivolumab be reimbursed as monotherapy for the adjuvant treatment of adult patients with stage IIB or IIC melanoma following complete resection, only if the following conditions are met:
		• Treatment with nivolumab should be reimbursed in adult patients with completely resected stage IIB or IIC cutaneous melanoma (as defined by the AJCC classification, eighth edition)
		• Treatment with nivolumab should be initiated within 12 weeks of surgery
		• Patient must not have received prior treatment beyond complete resection.
		• Reimbursement of nivolumab should be discontinued in patients who exhibit any of the following:
		  ○ clinical or radiological disease recurrence
		  ○ evidence of significant toxicity or adverse events potentially related to nivolumab
		• Patients should discontinue treatment following a maximum of 12 months of adjuvant nivolumab
		• Nivolumab should be prescribed in an outpatient oncology clinic and should be supervised and/or delivered in institutions with expertise in the delivery of immunotherapy
		• Nivolumab should not be combined with other anticancer drugs for melanoma.
		• The price of nivolumab should be negotiated so that the total cost of treatment does not exceed the drug program cost of treatment, with the least costly adjuvant therapy reimbursed for the treatment of adult patients with stage IIB or IIC melanoma following complete resection
		
		Guidance on sequencing:
		• In Checkmate-76K placebo-treated patients who experienced disease recurrence within 3 years after the last dose of placebo and nivolumab treated patients who experienced recurrence greater than 6 months and within 3 years after completing treatment, were eligible to cross over or

		rechallenge with nivolumab. Patients with recurrent, resectable disease were offered nivolumab for a maximum duration of 12 months. Patients in other solid tumours (e.g., lung, melanoma) are eligible for downstream PD-1/PD-L1 inhibitor provided that disease recurrence (whether locoregional or distant) occurs more than 6 months from the last dose of adjuvant PD-1/ PD-L1 inhibitor. pERC agreed with the clinical experts that the same principle used for other solid tumours could be applied in this case, according to the common standard clinical practice.

Pembrolizumab (Keytruda)	November 22, 2022	pERC recommends that pembrolizumab be reimbursed for the adjuvant treatment of adult and pediatric (12 years and older) patients with stage IIB or IIC melanoma following complete resection only if the following conditions are met:
		• Patients who have stage IIB or stage IIC melanoma (as defined by the American Joint Committee on Cancer 2017 classification, eighth edition).
		• Treatment with pembrolizumab should be initiated within 12 weeks of surgery.
		• Patients must not have received prior treatment beyond complete resection.
		• Reimbursement of pembrolizumab should be discontinued in patients who exhibit any of the following:
		  ○ clinical/radiological disease progression
		  ○ evidence of significant toxicity or adverse events potentially related to pembrolizumab.
		• Patients should discontinue treatment following a maximum of 17 cycles of adjuvant pembrolizumab.
		• Pembrolizumab should be prescribed in an outpatient oncology clinic and should be supervised and/or delivered in institutions with expertise in delivery of immunotherapy.
		• Pembrolizumab should not be used in combination with other anticancer drugs.
		• A reduction in price.
		• The feasibility of adoption of pembrolizumab must be addressed.
		
		Guidance on sequencing:
		• In KEYNOTE-716, patients in the placebo arm who experienced recurrence and patients in the pembrolizumab arm who experienced recurrence greater than 6 months after completing 17 cycles of treatment were eligible to cross over or rechallenge with pembrolizumab for up to 2 years. In other solid tumours (e.g., lung, melanoma), patients are eligible for downstream PD-1 or PD-L1 inhibitor provided that disease recurrence (whether locoregional or distant) occurs more than 6 months from the last dose of an adjuvant PD-1 or PD-L1 inhibitor.
		
		The clinical experts indicated that the same principle used for other solid tumours could be applied to the treatment setting for patients with stage II melanoma. Overall, the experts felt that stage II melanoma should not be treated any differently from stage III.
		
		pERC agreed with the clinical experts, noting the same principles used for other recommendations should be applied.

Stages IIIA, IIIB, IIIC, IIID, and IV melanoma		
Pembrolizumab (Keytruda)	August 1, 2019	pERC conditionally recommends the reimbursement of pembrolizumab (Keytruda) for the adjuvant treatment of patients with stage IIIA (limited to lymph node metastases of > 1 mm) to stage IIID (8th edition of the American Joint Committee on Cancer [AJCC] staging system) cutaneous melanoma.

		Disease must be completely resected; however, presence of regional lymph nodes with micrometastases after sentinel lymph node biopsy alone is allowed. Patients must have good performance status. Reimbursement is only recommended if the following conditions are met: • cost-effectiveness being improved to an acceptable level • feasibility of adoption being addressed (budget impact). Treatment with pembrolizumab should continue up to a maximum of 18 administrations or until unacceptable toxicity or disease recurrence, at which point the intent of further therapy (adjuvant or metastatic) should be re-evaluated based on extent of recurrence. **Guidance on optimal sequencing:** No evidence for optimal sequencing. pERC acknowledged that there is no direct comparative evidence investigating the efficacy and safety or the appropriate sequence of adjuvant therapies for patients with stage IIIA-D cutaneous melanoma. Further, the optimal sequencing of subsequent therapies for patients with metastatic melanoma after disease progression with adjuvant pembrolizumab is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognizes that provinces will need to address this issue upon implementation of a reimbursement recommendation for pembrolizumab and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.
Dabrafenib and trametinib in combination (Tafinlar and Mekinist in combination)	May 3, 2019	pERC conditionally recommends to reimburse dabrafenib (Tafinlar) in combination with trametinib (Mekinist) for the adjuvant treatment of patients with stage IIIA (limited to lymph node metastases of > 1 mm) to stage IIID (8th edition of the American Joint Committee on Cancer [AJCC] staging system) *BRAF*-mutated (all BRAD V600 mutations) cutaneous melanoma. Disease must be completely resected including in-transit metastases; however, presence of regional lymph nodes with micrometastases after sentinel lymph node biopsy alone is allowed. Patients must have good performance status. Reimbursement is only recommended if the following conditions are met: • cost-effectiveness being improved to an acceptable level • feasibility of adoption being addressed (budget impact). Treatment with dabrafenib plus trametinib should continue until disease recurrence, unacceptable toxicity, or up to a maximum of 12 months. **Guidance on optimal sequencing:** No evidence for optimal sequencing. pERC acknowledged that there is no direct comparative evidence investigating the efficacy and safety or the appropriate sequence of adjuvant therapies for patients with *BRAF*-mutated stage IIIA-D cutaneous melanoma. Further, the optimal sequencing of subsequent therapies for patients with *BRAF*-mutated metastatic melanoma after disease progression with adjuvant dabrafenib plus trametinib is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognizes that provinces will need to address this issue upon implementation of a reimbursement recommendation for dabrafenib plus trametinib, and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.
Nivolumab (Opdivo)	March 7, 2019	pERC recommends to reimburse nivolumab (Opdivo) only if the following conditions are met: • cost-effectiveness is improved to an acceptable level • feasibility of adoption is addressed (budget impact).

		If the aforementioned conditions are not met, pERC does not recommend reimbursement. Reimbursement should be for the adjuvant treatment of patients with completely resected stage IIIB/C/D and stage IV disease (8th edition of the American Joint Committee on Cancer (AJCC) melanoma staging system). Disease must be completely resected including in-transit metastases; however, presence of regional lymph nodes with micrometastases after sentinel lymph node biopsy alone is allowed. Eligible patients should continue treatment until disease progression or a maximum of 1 year, whichever comes first. **Guidance on optimal sequencing:** pERC concluded that the optimal sequencing of therapies for patients with metastatic melanoma after adjuvant treatment with nivolumab is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognizes that provinces will need to address this issue upon implementation of a reimbursement recommendation for nivolumab, and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.
Metastatic melanoma		
Nivolumab and Relatlimab (Opdualag)	February 21, 2024	pERC recommends that nivolumab and relatlimab be reimbursed for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma only if the following conditions are met: **Initiation** 1. Treatment with nivolumab and relatlimab fixed dose combination (FDC) should be reimbursed only in patients with all of the following characteristics: 1.1. Histologically confirmed unresectable stage III or stage IV (metastatic) melanoma 1.2. Have not received prior systemic therapy for unresectable or metastatic melanoma 1.3. Aged 12 years or older 1.4. Good performance status 2. Treatment with nivolumab and relatlimab FDC could be reimbursed in patients who had prior adjuvant or neoadjuvant anti-PD-1 or anti-CTLA-4 therapy if the therapy was completed at least 6 months before the date of recurrence. 3. Treatment with the nivolumab and relatlimab FDC should not be reimbursed in patients with: 3.1. Active brain metastases 3.2. Uveal melanoma 3.3. Active autoimmune disease **Renewal** 4. Treatment with nivolumab and relatlimab FDC may continue unless any of the following occurs: 4.1. Clinical or radiographic disease progression 4.2. Intolerable side effects that cannot be managed by dose interruption 5. Patients should be assessed for a response to treatment with nivolumab and relatlimab FDC every 2 to 3 months initially and then as per standard of care. **Discontinuation** 6. Treatment with nivolumab and relatlimab FDC should be discontinued upon the occurrence of any of the following: 6.1. Clinical or radiographic disease progression 6.2. Unacceptable toxicity **Prescribing**

		7. Nivolumab and relatlimab FDC should only be prescribed by clinicians who: 7.1. Have expertise in diagnosis and management of patients with melanoma 7.2. Are familiar with the toxicity profile associated with nivolumab and relatlimab FDC **Pricing** 8. A reduction in price 9. The feasibility of adoption of nivolumab and relatlimab must be addressed **Guidance on sequencing:** • pERC discussed the possible place in therapy of nivolumab and relatlimab, and concluded that nivolumab and relatlimab would be another alternative treatment option for patients who are not fit enough to receive nivolumab and ipilimumab combination or for patients who are ipilimumab ineligible and could have otherwise received nivolumab monotherapy, pembrolizumab monotherapy, or targeted BRAF therapy. • Based on the direct evidence, while pERC was confident in the PFS benefit of nivolumab and relatlimab compared to nivolumab monotherapy, pERC was less confident in the OS benefit since these results were not statistically significant and longer length of follow up is needed to confirm an OS benefit. • pERC acknowledged an established clinical benefit with nivolumab and ipilimumab combination for patients who are fit enough to endure the toxicities associated with this combination compared with nivolumab. While the RELATIVITY-047 study compared nivolumab and relatlimab to nivolumab monotherapy, there is no direct evidence to suggest a clinical benefit compared to nivolumab and ipilimumab combination. There remains uncertainty in the comparative efficacy of nivolumab and relatlimab compared to relevant comparators, including nivolumab and ipilimumab combination. pERC, however, acknowledged that according to clinical expert opinion, nivolumab and relatlimab has less toxicity than nivolumab and ipilimumab combination. • pERC recognized that nivolumab and relatlimab would be an alternative therapy in patients who progress on BRAF/MEK therapies used in the adjuvant setting. While pERC noted that the enrollment criteria permitted neoadjuvant or adjuvant IFN therapy with the last dose at least 6 weeks prior to randomization, pERC noted the infrequent and rare use of IFN therapy in neoadjuvant or adjuvant in Canada. Prior adjuvant or neoadjuvant anti-PD-1 or anti-CTLA-4 therapy should be followed as per RELATIVITY-047. • Eligibility to-retreatment: ○ pERC agreed with the clinical experts that re-initiation of treatment would be permitted for those who chose to take a treatment break but did not experience progression or unacceptable toxicity while on treatment on a case-by-case basis based on the discretion of the treating clinician. pERC agreed with the clinical experts that re-initiation would be considered in the case of progression while off therapy, and acknowledged that commonly, progression after a 6-month break is accepted as a guideline to reinstitute treatment.
Encorafenib (Braftovi) in combination with binimetinib (Mektovi)	July 26, 2021	pERC recommends that encorafenib in combination with binimetinib should be reimbursed for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation only if the following conditions are met: • Treatment with encorafenib-binimetinib should be initiated only in adults who have the following characteristics:

		○ histologically confirmed locally advanced unresectable or metastatic *BRAF* V600E and/or V600K-mutant cutaneous melanoma or unknown primary melanoma (stage IIIB, IIIC, or IV per AJCC) ○ no previous treatment received (treatment naive) or must have progressed on or after prior first-line immunotherapy for advanced or metastatic disease ○ performance status defined as: ▪ ECOG PS 0 to 1 ▪ adequate organ, bone marrow, and cardiac function, including left ventricular ejection fraction ≥ 50% by cardiac imaging and laboratory parameters. • Eligible patients should be identified through *BRAF* mutational analysis. • Treatment with the encorafenib-binimetinib combination should not be initiated in patients with: ○ untreated CNS lesions ○ uveal or mucosal melanoma ○ known positive serology for HIV, or an active hepatitis B or hepatitis C infection, or both ○ history of leptomeningeal metastases • Treatment with encorafenib-binimetinib may be continued unless any of the following occurs: ○ clinical or radiographic disease progression ○ intolerable side effects that are not responsive to dose reductions or dose delays. • Patients should be assessed for a response (as per RECIST 1.1) to treatment with encorafenib and binimetinib combination every 2 to 3 months. • Treatment with the encorafenib and binimetinib combination should be discontinued upon the occurrence of any of the following: ○ clinical or radiographic disease progression ○ unacceptable toxicity ○ development of adverse reactions that do not resolve despite dose delays or dose reductions. • If 1 component of the combination therapy is discontinued for toxicity or intolerance, the other drug in the combination should also be discontinued. • Encorafenib in combination with binimetinib should only be prescribed by clinicians who: ○ have expertise in diagnosis and management of patients with melanoma ○ are familiar with the toxicity profile associated with the encorafenib and binimetinib regimen. • Dosing of the encorafenib and binimetinib combination should be as follows: ○ encorafenib 450 mg once daily ○ binimetinib 45 mg twice daily Encorafenib in combination with binimetinib should not be more costly than the least costly *BRAFi/MEKi* combination regimen.
Nivolumab and ipilimumab (Opdivo and Yervoy in combination)	November 30, 2017	pERC recommends reimbursement of the combination of nivolumab plus ipilimumab conditional on the feasibility of adoption being addressed (budget impact). Reimbursement should be for patients with unresectable or metastatic melanoma regardless of *BRAF* status who are treatment-naive, with ECOG performance status 0-1 and with stable brain metastases, if present. Treatment should continue until unacceptable toxicity or disease progression.
Cobimetinib and vemurafenib (Cotellic and Zelboraf)	June 30, 2016	pERC recommends reimbursement of cobimetinib conditional on the cost-effectiveness being improved to an acceptable level. Reimbursement should be in combination with vemurafenib, for the treatment of patients with

		previously treated *BRAF* V600 mutation-positive unresectable stage III or stage IV melanoma who have a good performance status. Treatment should continue until unacceptable toxicity or disease progression. If brain metastases are present, patients should be asymptomatic or have stable symptoms. pERC does not recommend reimbursement of cobimetinib plus vemurafenib for the treatment of patients with previously treated *BRAF* V600 mutation-positive unresectable metastatic melanoma. **Guidance on sequencing:** *Patients With Disease Progression After Immune Checkpoint Therapy* pERC noted that there is no evidence to support or refute the use of cobimetinib plus vemurafenib in patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma with disease progression after treatment with an immune checkpoint inhibitor. Therefore pERC does not recommend reimbursement for cobimetinib plus vemurafenib in this group of patients. *Patients With Disease Progression on First-Line Vemurafenib* pERC noted that patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma with disease progression on first-line vemurafenib were excluded from the pivotal trial for this submission (coBRIM). The committee also considered evidence from a small phase I, non-comparative trial (BRIM7) that demonstrated poor response rates with cobimetinib plus vemurafenib in the cohort of patients whose disease had progressed while receiving vemurafenib. Therefore, pERC does not recommend reimbursement for cobimetinib plus vemurafenib for the treatment of patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma whose disease has progressed on first-line vemurafenib. *Time-Limited Need for Cobimetinib Plus Vemurafenib in Patients Currently Receiving First-Line Treatment With Single-Agent Vemurafenib* At the time of implementing a reimbursement recommendation for cobimetinib plus vemurafenib, jurisdictions may consider addressing the short-term, time-limited need to offer cobimetinib plus vemurafenib to patients currently receiving a single-agent *BRAF* inhibitor or MEK inhibitor for the first-line treatment of *BRAF* V600 mutation-positive unresectable or metastatic melanoma and whose disease has not progressed.
Nivolumab (Opdivo)	April 1, 2016	pERC recommends funding nivolumab (Opdivo) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of patients with unresectable or metastatic *BRAF* wild-type melanoma who are previously treated, with good performance status and who have stable brain metastases (if present). Treatment should continue until unacceptable toxicity or disease progression. However, pERC does not recommend funding nivolumab for the treatment of patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma. pERC does not recommend funding nivolumab for the treatment of patients with unresectable or metastatic melanoma who have previously received treatment with ipilimumab.
Pembrolizumab (Keytruda)	November 16, 2015	pERC recommends funding pembrolizumab (Keytruda) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be in patients with unresectable or metastatic melanoma (stage III or IV) who are naive to ipilimumab treatment and funding should also be in patients who have failed ipilimumab and, if *BRAF* mutation positive, have failed *BRAF* mutation targeted therapies. Treatment should be in patients with an ECOG performance status of 0-1, who have stable brain metastases (if present),

		using the 2 mg/kg dose every 3 weeks for 24 months or until disease progression, whichever occurs first.
Dabrafenib (Tafinlar) in combination with trametinib (Mekinist)	July 21, 2015	pERC recommends funding dabrafenib (Tafinlar) plus trametinib (Mekinist), conditional on cost-effectiveness being improved to an acceptable level. Funding should be for patients with *BRAF* V600 mutation-positive, unresectable, or metastatic melanoma in the first-line setting and who have an ECOG performance status of 0 or 1. Treatment is until disease progression. If brain metastases are present, patients should be asymptomatic or have stable symptoms.

AJCC = American Joint Committee on Cancer; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; PD-1 = programmed cell death 1 protein; PD-L1 = programmed cell death 1 ligand 1; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PS = performance status.

Table 2: CADTH Implementation Advice Panels on Melanoma

Date of publication	Implementation Advice
June 4, 2024	**Downstream treatment options following nivolumab-relatlimab** For patients without BRAF mutations: • The panel advises ipilimumab should be offered as a subsequent treatment option for patients with disease progression following nivolumab-relatlimab in the setting of unresectable or metastatic melanoma. For patients with BRAF mutations: • The panel advises that patients who have received BRAF targeted therapy as a first line treatment option in the metastatic setting should have the option to receive nivolumab-relatlimab in the second line setting, followed by ipilimumab in the third line setting.
December 17, 2019, funding recommendations, melanoma and adjuvant pembrolizumab	CDIAC considered clinician input and is offering the following recommendations for consideration by the CAPCA board: 1. That provinces expand the eligible population for adjuvant pembrolizumab to include resected stage IV, mucosal melanoma, and patients resected with in transit and satellite mets, which aligns with the eligible population for nivolumab. Clinicians consider these drugs to have similar enough efficacy in melanoma to want to be able to use either pembrolizumab or nivolumab. 2. That provinces not fund any immunotherapy (pembrolizumab or nivolumab) or *BRAF* targeted therapy for adjuvant treatment in ocular melanoma at this time, pending further evidence of benefit. Ocular melanoma has a different genetic profile than cutaneous melanoma; this recommendation aligns with a pERC recommendation suggesting that evidence of benefit in this patient population is lacking. 3. That provinces allow a one-time switch for *BRAF*-mutated patients between adjuvant therapies, within a time limit of 3 months after the initiation of therapy, but funded adjuvant therapy will be limited to 12 months total. This recommendation aligns with that previously approved for adjuvant nivolumab. 4. That provinces fund, on a time-limited basis, a switch from adjuvant interferon to adjuvant immunotherapy, for patients who are otherwise eligible for these regimens, at any time and to complete a year of therapy. This recommendation aligns with that previously approved for adjuvant nivolumab. 5. That high dose interferon be removed from the funding algorithm and noted as a historical treatment as it is no longer a Canadian standard of care for adjuvant therapy. This recommendation aligns with that previously approved for adjuvant nivolumab. 6. That provinces fund ipilimumab single agent therapy in the metastatic setting for patients who progress on adjuvant immunotherapy or progress within 6 month of last dose of pembrolizumab in the adjuvant setting. 7. That patients who receive pembrolizumab as potentially curative therapy and then relapse be eligible for downstream immunotherapy with nivolumab or pembrolizumab if equal or greater than 6 months have elapsed from the completion of adjuvant therapy. The provinces should continue to monitor the evolving evidence for IO re-treatment when IO is used in this potentially curative setting.

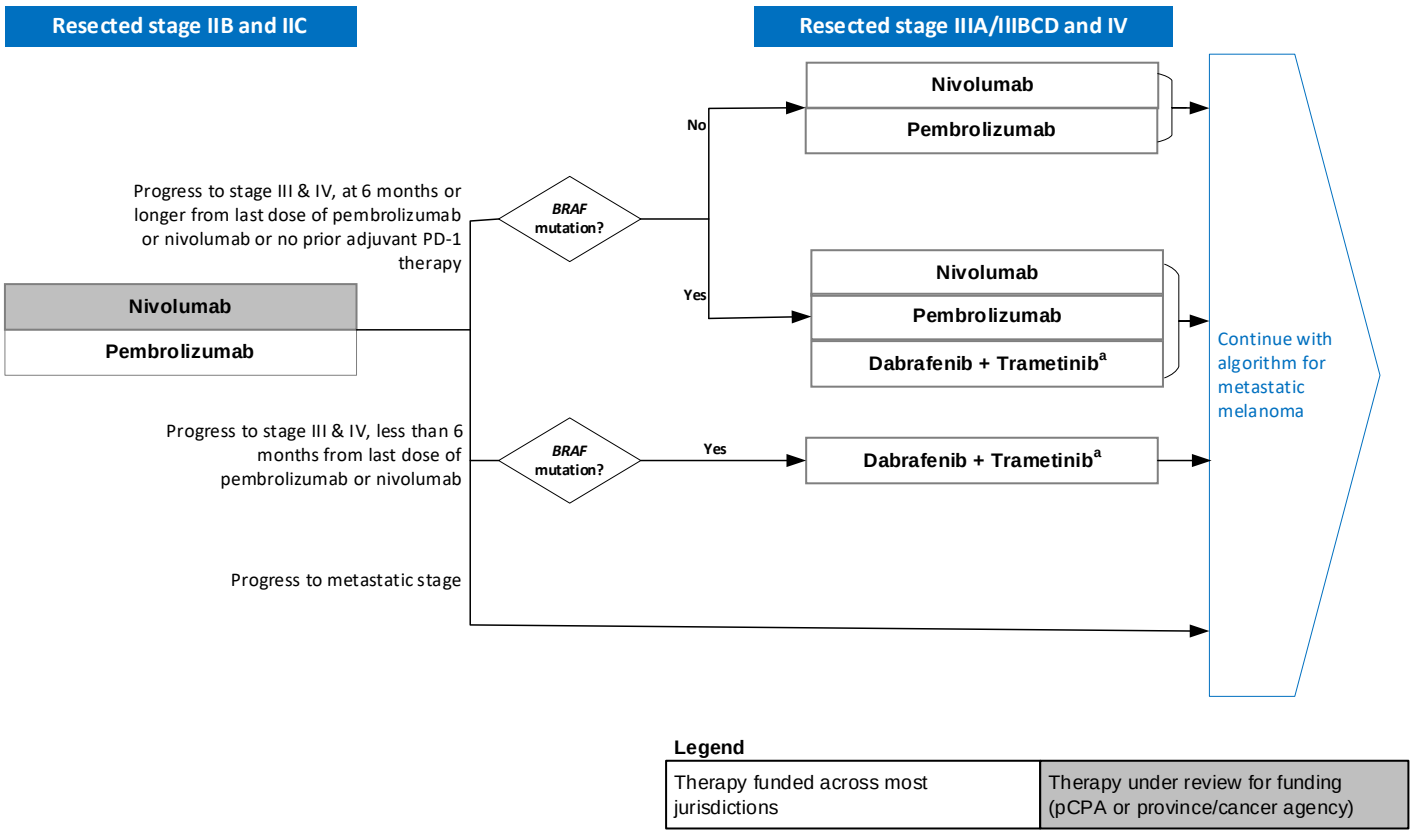
	8. That provinces fund combination immunotherapy (nivolumab + ipilimumab) for patients relapsing at ≥ 6 months after completing adjuvant immunotherapy. For patients relapsing ≥ 6 months after completing adjuvant immunotherapy and who are unfit for combination nivolumab + ipilimumab, that provinces fund single agent nivolumab or pembrolizumab immunotherapy as a treatment choice in the metastatic setting.
July 8, 2019, funding recommendations, melanoma and adjuvant nivolumab	CDIAC considered clinician input and is offering the following recommendations for consideration by the CAPCA board: 1. That provinces align with CheckMate 238 trial data and adhere to biweekly dosing of adjuvant nivolumab. 2. That provinces allow weight-based dosing of nivolumab with no dose cap as per the CheckMate 238 trial. 3. That provinces allow a one-time switch for *BRAF*-mutated patients between adjuvant therapies, within a time limit of 3 months after the initiation of therapy, but funded adjuvant therapy will be limited to 12 months total. 4. That provinces fund, on a time-limited basis, a switch from adjuvant interferon to adjuvant immunotherapy or dabrafenib-trametinib, for patients who are otherwise eligible for these regimens, at any time and allow a full year of therapy. 5. That provinces not fund a switch to cobimetinib-vemurafenib in *BRAF*-positive patients. 6. That provinces fund ipilimumab single agent therapy in the metastatic setting for patients who progress on adjuvant immunotherapy. 7. That provinces fund combination immunotherapy (nivolumab + ipilimumab) for patients relapsing on or any time after dabrafenib + trametinib therapy. 8. That provinces allow retreatment with *BRAF*-targeted therapy if the treatment free interval is ≥ 6 months from the completion of adjuvant *BRAF* therapy. 9. That provinces fund dabrafenib + trametinib in the rare instances where a BRAF positive patient relapses, and would otherwise be eligible for this therapy, after adjuvant immunotherapy. 10. That high dose interferon be removed from the funding algorithm and noted as a historical treatment as it is no longer a Canadian standard of care for adjuvant therapy. 11. Provinces should expand the eligible population for adjuvant nivolumab to include stage IIIA (with node metastases > 1 mm) — this will correspond to the population included in the pembrolizumab study (clinicians consider these drugs therapeutically equivalent — so makes no sense to have them available in different populations). NOTE: There does not currently exist data on retreatment with immunotherapy after adjuvant therapy, nor the timing of such. There is data that suggests that metastatic patients progressing off immunotherapy can respond by restarting the same immunotherapy. Provinces will likely benefit from having a standard time interval for restarts on all immunotherapies and CAPCA and CADTH have proposed a process to support said standardization. Information will be used to inform these, and subsequent immunotherapy recommendations as it becomes available.

CAPCA = Canadian Association of Provincial Cancer Agencies; CDIAC = Cancer Drug Implementation Advisory Committee; OI = osteogenesis imperfecta; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for Adjuvant Therapy for Melanoma

This is not a comprehensive list of all available treatments nor a treatment algorithm. Drugs available and funded through other mechanisms (e.g., clinical trials, manufacturer's compassionate access program, private payors) are not included.

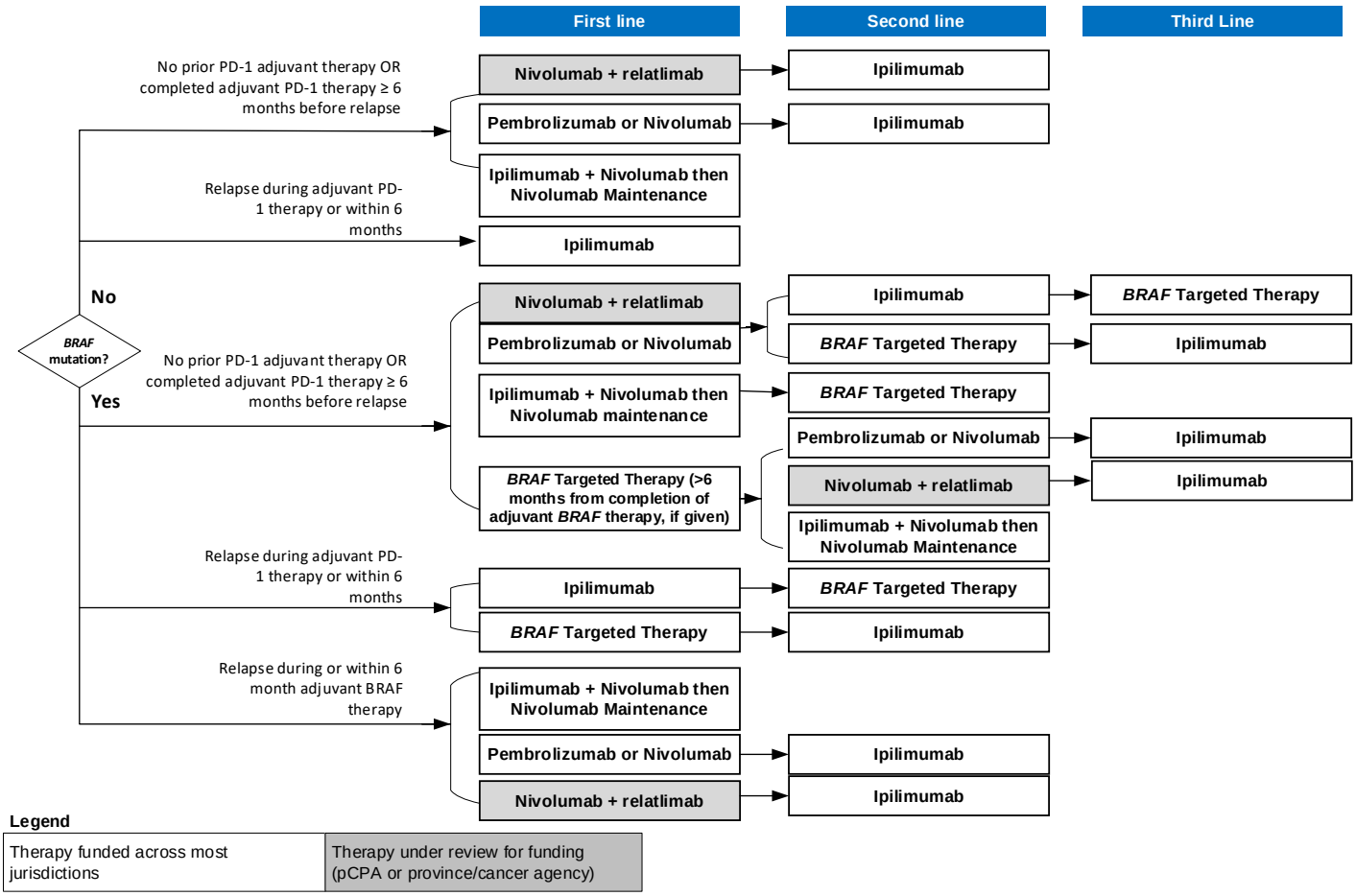


pCPA = pan-Canadian Pharmaceutical Alliance.
Notes: Ocular melanoma is excluded.
High-dose interferon is a historical treatment that is no longer used in the Canadian treatment landscape for adjuvant therapy of patients with high-risk melanoma.
All drugs may be subject to additional funding criteria within provincial jurisdictions.
[a] For cutaneous melanoma only. Also excludes resected stage IV melanoma.

Alt text: The algorithm provides an overview of various options for adjuvant therapy for melanoma. Treatment options for resected stage IIB and IIC melanoma include nivolumab and pembrolizumab. Treatment options for resected stage IIIA/IIIBCD and IV include nivolumab, pembrolizumab, and dabrafenib with trametinib.

Figure 2: Provisional Funding Algorithm Diagram for Metastatic Melanoma

This is not a comprehensive list of all available treatments nor a treatment algorithm. Chemotherapy, as a last line of treatment, is not represented on the algorithm. Drugs available and funded through other mechanisms (e.g., clinical trials, manufacturer's compassionate access program, private payors) are not included.



pCPA = pan-Canadian Pharmaceutical Alliance; PD-1 = programmed cell death 1 protein.

Notes: BRAF-targeted therapy options include dabrafenib-trametinib, cobimetinib-vemurafenib and encorafenib-binimetinib. All drugs may be subject to additional funding criteria within provincial jurisdictions.

If PD-1 therapy (initiated either as nivolumab/relatlimab, a single-drug, or maintenance following combination immunotherapy) is stopped after 2 years or at time of best response without evidence of disease progression, then therapy may be restarted at relapse as the same line of therapy. Re-treatment with ipilimumab/nivolumab combination immunotherapy is not funded. All drugs may be subject to additional funding criteria within provincial jurisdictions.

Alt text: The algorithm provides an overview of various treatment options for metastatic melanoma. First line options include nivolumab with relatlimab, pembrolizumab, nivolumab, ipilimumab, ipilimumab with nivolumab, and BRAF targeted therapy. Second line options include ipilimumab, BRAF targeted therapy, pembrolizumab, nivolumab, nivolumab with relatlimab, and ipilimumab with nivolumab. Third line options include BRAF targeted therapy and ipilimumab.

Description of the Provisional Funding Algorithm

Adjuvant Therapy for Melanoma (Depicted in Figure 1)

Resected Stage IIB and IIC

Pembrolizumab and nivolumab are indicated as adjuvant treatments for patients with stage IIb and IIc melanoma after complete resection. Nivolumab is currently under review for funding.

Resected Stage IIIA, III, IIIB, IIIC, IIID, and IV

In the adjuvant setting of stage IIIA, IIIB, IIIC, IIID, and IV, the treatment options depend on if there has been prior use of pembrolizumab in stage IIB and IIC, as well as if there is BRAF mutation.

- If the progression or relapse has occurred within 6 months of pembrolizumab treatment, no additional programmed cell death 1 protein (PD-1) inhibitor or programmed cell death 1 ligand 1 (PD-L1) inhibitor would be funded in stage III or IV of the adjuvant setting. However, if the individual has a confirmed BRAF mutation, dabrafenib-trametinib is an option for cutaneous melanoma, excluding for those with resected stage IV melanoma.
- If the progression or relapse has occurred at 6 months or longer (or in cases with no prior use of PD-1 inhibitor or PD-L1 inhibitor), then treatment options also depend on BRAF mutation. If there is no BRAF mutation, the available options are nivolumab and pembrolizumab. If BRAF mutation is present, the available options are nivolumab, pembrolizumab, and dabrafenib-trametinib. However, dabrafenib-trametinib is only for cutaneous melanoma and excludes individuals with resected stage IV melanoma.

Note that ocular melanoma is excluded in this funding algorithm. Also, it would be rare that individuals would progress from stage II to stage III for additional treatment options. If this does occur, only individuals who have had a disease-free period of at least 6 months or longer since the last dose of an adjuvant PD-1 or PD-L1 inhibitor would be eligible for treatment options funded in the stage IIIA, IIIB, IIIC, IIID, and IV adjuvant setting.

For individuals whose disease progresses to advanced or metastatic melanoma after receiving adjuvant treatments in resected stage II, III, or IV, please refer to the algorithm for metastatic melanoma for funding options.

Metastatic Melanoma (Depicted in Figure 2)

The treatment options in the metastatic setting differ depending on the status of BRAF mutation.

No BRAF Mutation

No Prior PD-1 Adjuvant Therapy or Completed Adjuvant PD-1 Therapy 6 Months or More Before Relapse

For individuals with no BRAF mutation and with no prior PD-1 adjuvant therapy or who completed adjuvant PD-1 therapy 6 months or more before relapse, the first-line options can be either pembrolizumab, nivolumab or nivolumab-relatlimab, followed by the second-line

option of ipilimumab. Nivolumab-relatlimab is under review for funding. Another first-line option can be ipilimumab with nivolumab followed by nivolumab maintenance therapy.

Relapse During Adjuvant PD-1 Therapy or Within 6 Months

For individuals with no BRAF mutation who relapse during adjuvant PD-1 therapy or within 6 months of therapy, the first-line option in the metastatic setting is ipilimumab.

With BRAF Mutation

No Prior PD-1 Adjuvant Therapy or Completed Adjuvant PD-1 Therapy 6 Months or More Before Relapse

For individuals with BRAF mutation and with no prior PD-1 adjuvant therapy or who completed adjuvant PD-1 therapy 6 months or more before relapse, there are 3 available first-line options, of which will determine subsequent second-line or third-line options:

- **Pembrolizumab, nivolumab or nivolumab-relatlimab:** If individuals have either pembrolizumab, nivolumab or nivolumab-relatlimab as a first-line option, the second-line option can be ipilimumab or BRAF-targeted therapy. For those who have received ipilimumab as a second-line option, the third-line option is BRAF-targeted therapy. For those who have received BRAF-targeted therapy as a second-line option, the third-line option is ipilimumab. Nivolumab-relatlimab is under review for funding.
- **Ipilimumab-nivolumab then followed by nivolumab maintenance:** Alternatively, individuals may begin the first-line option of ipilimumab-nivolumab, which is followed by nivolumab maintenance therapy. Following this first-line option, the second-line option is BRAF-targeted therapy.
- **BRAF-targeted therapy:** Individuals may begin with BRAF-targeted therapy as a first-line option. Available BRAF-targeted therapy options include dabrafenib-trametinib, encorafenib-binimetinib, and cobimetinib-vemurafenib. If given in this setting, these individuals must have completed prior adjuvant BRAF therapy more than 6 months previously. The second-line option would be a choice of pembrolizumab, nivolumab or nivolumab-relatlimab with a subsequent third-line option of ipilimumab. Another second-line option would be ipilimumab-nivolumab followed by nivolumab maintenance therapy. Nivolumab-relatlimab is under review for funding.

Relapse During Adjuvant PD-1 Therapy or Within 6 Months

For individuals with BRAF mutation who relapse during adjuvant or within 6 months of PD-1 therapy, the first-line options would be a choice between ipilimumab or BRAF-targeted therapy. If the first-line option is ipilimumab, then the second-line option is BRAF-targeted therapy. If the first-line option is BRAF-targeted therapy, the second-line option is ipilimumab.

Relapse During Adjuvant BRAF Therapy or Within 6 Months

For individuals with BRAF mutation who relapse during or within 6 months of adjuvant BRAF-targeted therapy, the first-line option would be a choice of pembrolizumab, nivolumab or nivolumab-relatlimab with a subsequent second-line option of ipilimumab. Another first-line option would be ipilimumab-nivolumab followed by nivolumab maintenance therapy. Nivolumab-relatlimab is under review for funding.

Additional Remarks

Six-Month Retreatment Interval

These algorithms have adopted guidance from pERC and recommendations from previous panel algorithm projects conducted by CDIAC in July 2019 and December 2019 on a cut-off re-treatment interval of 6 months. Individuals are generally not eligible for re-treatment with drugs from the same drug categories if they have disease progression within 6 months of treatment completion. The reimbursement of ipilimumab-nivolumab in the first-line metastatic setting in patients who progress during or within 6 months of adjuvant anti-PD-1 therapy is being addressed in another reimbursement review: Nivolumab and Ipilimumab | CADTH.